II. REMARKS RE CLAIMS

By this response, the original claims 1-35 have been cancelled and claims 36-74 are substituted, of which claims 36, 39, 42, 48,54,57,61 and 68 are independent claims and the remaining 31 are dependent claims.

Five independent claims and 30 dependent claims were originally presented and the requisite fees were paid. Submitted herewith is a check for $138.00 to cover the small entity fee for 3 additional independent claims at $43.00 each and the $9.00 fee for one additional dependent claim in excess of the original 30 now presented.

It is believed that the present claims are free from the 35 U.S.C. §112, second paragraph rejections set forth in the office action. In particular, the new method claims *do* each include a step of quantifying the amount of β-hydroxybutyrate alone, combined β-hydroxybutyrate and acetoacetate, or total ketone bodies, as the case may be, that are present in the sample by reference to a visual color standard or by an electrochemical, fluometric or spectrophotometric measurement.

As to acetoacetate and acetone, these are, with hydroxybutyrate, the totality of ketone bodies present in such bodily fluids as urine, blood, saliva, etc., as the specification and the prior art clearly teach. The present application contemplates the *measurement* of any of hydroxybutyrate alone, combined hydroxybutyrate and acetoacetate, or total ketone bodies, and the ensuing *correlation* of the measurement made to the concentration of the measured substance in the sample. As is known in the art, concentration of whichever substance one chooses to measure can, in each instance, be correlated to fat loss by resort to well-established numerical tables.

The words "optionally together with acetoacetate and/or acetone" no longer appear in the claims.

III. THE 35 U.S.C. §102(b) / 35 U.S.C. §103(a) REJECTION

This rejection is based upon Ouyang U.S. Patent 5,902,731.

Ouyang does not *anticipate* applicant's invention under 35 U.S.C. §102(b) as postulated for at least the following reasons:

1. Ouyang's reagent and test strip have the objective of measuring β -hydroxybutyrate in *hemoglobin*-containing biological fluids. The reagent contains a nitrite for the specific purpose of "suppressing" hemoglobin. Application's test strip does not contain nitrite or hemoglobin suppressor of any type.

Applicant's objective is to supply a test strip that can be used to test urine and other sample fluids that can be obtained *without* the use of needles, syringes and the like, and without the invasive procedures that are requisite to obtaining blood, blood serum and other such fluids. A test strip that is capable of obtaining useful information when dipped in urine is of particular value to people who wish to monitor their own weight loss progress. Such a test strip, though especially directed toward those on weight loss programs, is also beneficial to diabetics and others afflicted with disorders where daily monitoring of ketosis states is desirable because it removes the need for relentless day-to-day drawing of blood samples accompanied in many cases by needle marks, bruising, skin discolorations and other disfigurements that rapidly become permanent if repeated daily over months and years.

2. The test strip of Ouyang is a multi-layer device comprising *at least* a support layer, a test pad and an overlayer. The purpose of the overlayer is to carry at least part of the nitrite ingredient which reacts with hemoglobin and renders it "harmless to the assay" (col. 5, lines 46-47). The test pad is usually made of a bibulous material and it carries the reagents which

co-act to measure the hydroxybutyrate content of the sample. Ouyang discloses a test pad that is very small in relation to the strip and the single example shows application to that test pad of *one drop* of blood. (col.5, lines 42-43).

By contrast, appellant's strip consists of a backing layer and a test layer of the same dimension as the backing layer. The test layer is uniformly impregnated throughout its full dimension with the mixed chemicals for measuring hydroxybutyrate alone or those for measuring hydroxybutyrate and acetoacetate combined, or those for measuring total ketone bodies. To test a sample the *entire* strip is dipped in the sample, saturating the test layer.

3. Ouyang contains *no* suggestions for measuring combined hydroxybutyrate and acetoacetate in *any* sample, whether blood, urine or another biological fluid. Ouyang likewise contains *no* suggestion for measuring total ketone bodies(i.e., combined acetone, acetoacetate and hydroxybutyrate) in *any* sample of biological fluid.

Applicant by contrast discloses that the same test layer may be impregnated with any of three reagent mixtures, i.e., a mixture for measuring hydroxybutyrate alone, a mixture for measuring combined hydroxybutyrate and acetoacetate *or* a mixture for measuring total ketone bodies. Applicant's reagent layer, when dried and affixed to a backing layer, may be separated into strips, which are usable by merely dipping each into the sample such as urine, or another noninvasively available fluid, e.g. saliva.

4. Ouyang does not disclose or appreciate that blood-- the one and only sample of choice according to his disclosure--contains relatively *little* chloride content as compared to urine. Ouyang does not appreciate and does not teach that tests for measuring hydroxybutyrate conducted on urine samples often give false negative results due to the high chloride ion

content of urine.

The disclosure by Ouyang of β-hydroxybutyrate dehydrogenase from *Pseudomonas* does not, "inherently" or otherwise, produce applicant's sensitive and specific measurement of hydroxybutyrate in urine because Ouyang not only fails to recognize the problem, but has no basis for recognizing or teaching how to solve it.

Only applicant has discovered and teaches that (i) either β-hydroxybutyrate dehydrogenase that is from a source such that it is uninhibited by chloride ions, such as *Alcaligenes* (not mentioned by Ouyang) *or* (ii) using β-hydroxybutyrate dehydrogenase from a source such that it *is* inhibited by chloride ions (such as the *Pseudomonas* mentioned in Ouyang), *but* using it in substantial excess--i.e. 10 to 20 times the concentration that is needed when the β-hydroxybutyrate is from a source such that it is not inhibited by chloride ions--will solve the false negative test result problem. While the Examiner may be tempted to counter by pointing to Ouyang's Table I as showing the presence in the "reagent for test pad" of Table 1, Example 1 of "50,000 U" of β-HBD, it is important to recognize that the Ouyang disclosure, in specifying a large amount of β-hydroxybutyrate dehydrogenase in the "reagent"

(i) is *not talking about the concentration of this ingredient on the test pad,* which concentration is wholly *uncertainable* from the Ouyang disclosure (Example 1);

(ii) is intending the "reagent" to be used in a test pad for analyzing *one drop* of blood, and *not* as an impregnating solution for a strip to be dried and

later dipped to saturation in a urine sample–in order to make the hydroxybutyrate measurement,

(iii) neither intends to, nor does, give any guidance about measuring hydroxybutyrate in urine samples; and

(iv) does not even suggest that the disclosed reagent combination *could* be used to measure hydroxybutyrate content of urine samples, much less suggest precautions to be taken or modifications to be made *if it were* so used.

5. Ouyang's Table I *does* minimally recognize pH level in its listing of the components of the "Reagent for the Test Pad" in column 6. Thus in parenthesis following "Tris (hydroxymethyl) Aminomethane, the words, "Adjust pH to 8.5 by adding 6M HCl" appear. However, it is far from clear whether such an adjustment in a "reagent" bath would insure that the reaction, performed on a test pad earlier exposed to the bath, of one drop of blood with the ingredient mix on that test pad would proceed in the pH region *above* pH 8.5 where the β-hydroxybutyrate measurement reaction occurs.

Assuming that the reaction pH requirement when the sample *is* one drop of blood is met by Ouyang's disclosure, it is important to recognize that the relatively massive sample of urine that applicant's strips are designed to interact with requires careful control of the pH of the strip impregnating solution to ensure that the reaction between the reagent mix on the strip and the urine into which the strip is dipped occurs expeditiously and fully at a pH *above* 8.5.

Certainly Ouyang gives no unequivocal teaching regarding reaction pH and perhaps, if one considers that the impregnating agents in the Ouyang sample pad are necessarily present in greatly excess over the one drop of sample, this is adequate to the description of the narrow invention described--i.e. the measurement of hydroxybutyrate *alone* in hemoglobin-containing samples.

Ouyang, however, makes no effort to teach the requirements of test strips made by immersing the whole test strip in reagent solution, drying it and then immersing it again in sample. When one considers that Ouyang's disclosure is limited by the nature of the test strip reagent pad and one drop sample described, making it unnecessary for Ouyang to be concerned about any need to control reaction pH, it becomes clear that Ouyang's system is very different from that of Applicant.

To sum up, Applicant has shown that Ouyang is *not a* 35 U.S.C. §102(b) reference because Ouyang's invention as disclosed differs markedly from Applicant's invention. Ouyang's invention is the measurement of hydroxybutyrate *only* in one-drop, *hemoglobin-containing* biological samples.

Applicant's invention is a test strip and method for measuring hydroxybutyrate alone *or* combined hydroxybutyrate and acetoacetate, *or* total ketone bodies, which is especially designed for weight loss monitoring, albeit useful in other contexts.

In showing the lack of *identity* between Ouyang's strip and method and applicant's, applicant has also shown that the differences between the two are vast and certainly not of the sort that make the claimed subject matter here even marginally "such that the subject matter as a whole would have been obvious at the time the invention was made to a person having

ordinary skill" (35 U.S.C. §103) in the art of measuring ketone bodies in human biological samples.

The different measuring strips, the different samples, the different intended uses of the different strips, the different precautions needed for measuring hydroxybutyrate alone in the hemoglobin- containing fluids of Ouyang versus those for measuring hydroxybutyrate alone in urine a shown by Applicant are clearly *vast*. Furthermore, Ouyang teaches *nothing* whatever about simultaneous measurement of *both* hydroxybutyrate and acetoacetate in *any* biological fluid and *nothing* whatever about simultaneous measurement of total ketone bodies in *any* biological fluid. Indeed, Ouyang does not even exhibit interest in making either of the latter two measurements.

The rejection is without merit and its withdrawal is respectfully requested.

CONCLUSION

Applicant has striven diligently to present new claims that are free of the rejections advanced and believes them to be in condition for allowance, which is therefore respectfully requested. Should the Examiner be of a different view, based upon issues of claim wording or claim form, she is courteously requested to telephone Applicant's counsel at the number given below, in an effort to expedite this prosecution.

Respectfully submitted,

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